

REMARKS

Status of the Claims:

Claims 1-47 were pending in the application. By this amendment, claims 1-7, 9-12, 14-35 and 47 are amended, and claims 13 and 36-46 are cancelled without prejudice or disclaimer.

Claims 1-13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,895,726 (Curtet) in view of U.S. Patent No. 6,074,670 (Stamm). The rejection is respectfully traversed.

Substance of the Interview:

Applicants gratefully acknowledge the interview conducted September 20, 2005.

During the interview, the examiner acknowledged that the *in vivo* data presented in the proposed Bobotas Declaration establishes unexpected results in that the claimed pharmaceutical formulations achieve greater bioavailability than those of the prior art, and this is achieved with lower concentration of hydrophilic polymer than that taught by Stamm (the '670 patent).

It was further agreed that patentability would be further supported by amendments reciting that the claimed composition is in granule form and/or by reciting the relative concentrations of the fenofibrate and the binder by reference to their mass ratio (e.g., as in claim 21).

In order to expedite examination, Applicants agreed to withdraw claims 36, 37, and 46, directed to methods of preparing compositions; and claims 38-45 directed to aqueous suspensions, without prejudice or disclaimer.

Supplemental Information Disclosure:

Applicants submit herewith a Supplemental Information Disclosure Statement citing additional art. Applicants do not believe that the newly cited art is more relevant than that relied upon in the outstanding rejection; however, Applicants do not wish to leave any question as to their compliance with 37 CFR § 1.56.

In the interest of expediting examination, Applicants address EP 0 793 958 to Keil et al. Since this application is in German, a full translation of the specification

has been provided herewith. The Keil reference discloses fenofibrate compositions. The compositions are fabricated by a wet granulation method, which produces a composition lacking the granular structure of the instant claims, which require a neutral core coated with fenofibrate, surfactant and binder.

The Keil fenofibrate compositions require cross-linked polyvinylpyrrolidone. See, e.g., page 9, second paragraph ("... in the process of the invention cross-linked polyvinylpyrrolidone must be obligatorily also mixed in."). Cross-linked polyvinylpyrrolidone is not water soluble, which is a requirement of the solubilization adjuvant (binder) of the present invention.

More importantly, the Keil fenofibrate compositions are not granular compositions that comprise a neutral microgranule core. Indeed, Keil expressly distinguishes over a reference describing such a structure. See page 9, second paragraph (distinguishing EP A1 256 933, the European equivalent to U.S. Patent No. 4,800,079, of record).

Keil reports that the resulting formulation "yielded no significant deviation between the present fenofibrate preparation produced in accordance with the invention and the one produced according to example 1 of EP patent 330 532." See page 13, final paragraph. EP '532 corresponds to Curtet (the '726 patent). The present invention, on the other hand, provides for a surprising and unexpected increase in bioavailability as compared to Curtet, as explained to the examiner in the interview, and as further elucidated below.

Thus, Applicants respectfully submit that the newly-cited Keil reference neither anticipates nor renders obvious the present invention.

The Present Rejection:

As noted above, claims 1-13 presently stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Curtet (the '726 patent) in view of Stamm (the '670 patent). As demonstrated to the examiner in the interview, the present invention surprisingly yields greater fenofibrate bioavailability than commercial embodiments of the Curtet and Stamm patents. In the fenofibrate art, increased bioavailability is very important to reduce the dosage of the drug (and thereby reduce

the potential side effects). The following is a short history of fenofibrate dosage forms, which demonstrates this importance.

Fenofibrate is a well-known drug used for the treatment of hyperlipidemia, hypertriglyceridemia and hypercholesterolemia. Fenofibrate has poor water solubility, and its absorption in the digestive tract is limited. In the mid-1980's, the daily dose of fenofibrate was as much as 300 mg (3 X 100 mg) (see Attachment A, the product insert for LIPIDIL® fenofibrate capsules), which resulted in side effects. Since then, much research has been devoted to decreasing the effective dose of fenofibrate while increasing the bioavailability of the drug. One approach was to decrease the particle size of fenofibrate by micronization, thus permitting faster dissolution and associated absorption in the upper GI tract (fenofibrate is poorly absorbed in the lower GI tract). See U.S. Patent No. 4,800,079.

Curtet's '726 patent showed another approach to reduce the daily dose of fenofibrate. The '726 patent describes capsules of a therapeutic composition containing a co-micronized mixture of fenofibrate and a solid surfactant. This technology was employed in TRICOR® fenofibrate capsules, which were available in 67 mg, 134 mg and 200 mg strengths, and were marketed by Abbott Laboratories. (See Attachment B, the product insert for TRICOR® fenofibrate capsules; this product has been discontinued.) According to the product insert, one 67 mg capsule containing co-micronized fenofibrate was bioequivalent to one 100 mg capsule containing non-micronized fenofibrate (i.e., a LIPIDIL® capsule). Thus, the effective daily dose of fenofibrate was reduced from 300 mg to 200 mg.

The '726 patent was listed by its manufacturer, Abbott Laboratories, Inc., in the FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the "Orange Book") as covering TRICOR® fenofibrate capsules. (See Attachment C, the 2002 Orange Book listing for TRICOR® fenofibrate capsules.) Thus, according to the manufacturer, TRICOR® fenofibrate capsules are a commercial embodiment of the '726 patent.

Stamm's '670 patent reports that, while the '726 patent¹ was an improvement over the 300 mg daily dose of fenofibrate, the '726 patent technology "suffers from

¹ The '670 patent refers to the European equivalent of the '726 patent, namely EP-A-0330532.

several disadvantages.” (Column 1, lines 66-67.) The ‘670 patent deemed itself an improvement over the formulations of the ‘726 patent.

The ‘670 patent discloses a fenofibrate composition containing 5-50% fenofibrate, optionally co-micronized with 0-10% of a surfactant, and 20-60% of a hydrophilic polymer. The claims of the ‘670 patent require 20-45% fenofibrate, optionally co-micronized with 0.1-3% of a surfactant, and 20-45% of a hydrophilic polymer.

The manufacturer introduced a second-generation TRICOR® product, in the form of tablets in 54 mg and 160 mg strengths. (See Attachment D, the product insert for TRICOR® fenofibrate tablets, 54 mg and 160 mg; also discontinued.) According to the product insert, the 160 mg TRICOR® fenofibrate tablets are bioequivalent to 200 mg fenofibrate capsules (i.e., a TRICOR® capsule). Thus, the effective daily dose of fenofibrate was reduced from 200 mg to 160 mg.

The ‘670 patent was listed in the Orange Book by the manufacturer as covering TRICOR® fenofibrate tablets, 54 mg and 160 mg. (See Attachment C, the 2002 Orange Book listing for TRICOR® fenofibrate tablets, 54 mg and 160 mg.)² Thus, according to the manufacturer, TRICOR® fenofibrate tablets, 54 mg and 160 mg, are a commercial embodiment of the ‘670 patent.³

The LIPIDIL® and TRICOR® family of products described above demonstrate an evolution from higher to lower maximum daily doses of fenofibrate (first 300 mg per day, then 200 mg per day, then 160 mg per day, then 145 mg per day).

The present invention furthers the advances made by the prior fenofibrate formulations covered by the ‘726 patent and the ‘670 patent. Unlike the ‘670 patent formulations, however, the pharmaceutical formulations of the present invention increase the percentage of fenofibrate, and decrease the percentage of binder. The claimed pharmaceutical compositions constitute more fenofibrate relative to binder than the compositions of the ‘670 patent.

² The ‘726 patent is also listed; however, the ‘726 patent claims only cover capsules, not tablets, and therefore the ‘726 patent is not relevant to this product.

³ Subsequent to the introduction of 54 mg and 160 mg TRICOR® fenofibrate tablets, the manufacturer introduced a third-generation TRICOR® product in the form of tablets in 48 mg and 145 mg strengths (see Attachment E, the product insert for TRICOR® fenofibrate tablets, 48 mg and 145 mg), thus again reducing the maximum daily dose of fenofibrate, from 160 mg to 145 mg. The ‘670 patent is not listed in the Orange Book for this third-generation product.

Surprisingly, the combination of a higher percentage of fenofibrate and a lower percentage of binder results in increased bioavailability, and a reduction in the amount of fenofibrate necessary for effective treatment. See Bobotas Declaration submitted herewith. Specifically, the claimed formulations provide greater bioavailability on a per-milligram basis than the TRICOR® formulations covered by the '726 patent and the '670 patent.

A commercial embodiment of the present invention is ANTARA® fenofibrate capsules (See Attachment F, the product insert for ANTARA® fenofibrate capsules), marketed by Reliant Pharmaceuticals, Inc. According to the product insert, 130 mg ANTARA® fenofibrate capsules are bioequivalent to 200 mg fenofibrate capsules (i.e., a TRICOR® capsule). Thus, with ANTARA®, the maximum daily dose of fenofibrate has been advantageously reduced to 130 mg.

The Bobotas Declaration submitted herewith supports the foregoing. The Bobotas Declaration shows that a commercial embodiment of the claimed invention, 130 mg ANTARA® capsules, has significantly greater bioavailability than a commercially available embodiment of the '726 patent. Specifically, the Bobotas Declaration establishes that, after a single dose, 130 mg ANTARA® capsules have 25.5% greater bioavailability (on a per milligram basis) than 200 mg TRICOR® capsules, which are commercial embodiments of the '726 patent; and at steady state, 130 mg ANTARA® capsules have 37.3% greater bioavailability on a per milligram basis. Bobotas Declaration, ¶¶ 8 and 12.

Likewise, the Bobotas Declaration provides comparative data relative to the '670 patent. Here, Dr. Bobotas compares 120 and 144 mg capsules of the claimed invention to 160 mg TRICOR® tablets, a commercial embodiment of the '670 patent. The Declaration establishes that the embodiments of the claimed invention, i.e., 120 mg and 144 mg capsules, show a 20.0% and 14.7% greater bioavailability, respectively, on a per-milligram basis relative to 160 mg TRICOR® tablets. Bobotas Declaration, ¶ 16.

Applicants respectfully submit that the above remarks and the Bobotas Declaration demonstrate that the present invention achieves surprising and unexpected results. Neither the '670 patent nor the '726 patent teach or suggest that a combination of a higher percentage of fenofibrate and a lower percentage of

polymer would produce an increase in bioavailability, and a decrease in the amount of fenofibrate necessary for effective treatment. This effect is only seen in the claimed invention.

The Examiner has asserted that the '670 patent suggests using hydrophilic polymer in a fenofibrate formulation in the range of 5-40% (citing Col 6, lines 30-40). This is not an accurate reading of the '670 patent. The cited section describes the formulation of a suspension. That suspension is then sprayed onto neutral granules. The composition of the suspension is quite different than the final composition of the pharmaceutical formulation (i.e., the coated granules); and so it cannot be said that this embodiment of the '670 patent teaches or suggests the claimed pharmaceutical formulation, which is in the form of granules.

Indeed, as Applicants have shown, the cited references teach away from the present invention. The '670 patent teaches that to enhance bioavailability and thereby produce an effective formulation of reduced dosage, one must use at least 20% by weight hydrophilic polymer by weight of the composition ('670, col. 3, lines 11-23); and fenofibrate up to 50% by weight of the composition ('670, col. 5, lines 3-4). In contrast, Applicants' claimed granules contain 2-15% by weight of binder, and at least about 60% by weight fenofibrate; and, most surprisingly, in doing so the invention achieves substantially greater bioavailability and more rapid dissolution. This is the hallmark of non-obviousness and thus, patentability.

CONCLUSION

The Bobotas Declaration and the above remarks establish patentability for at least two reasons. First, the claimed compositions are contrary to conventional wisdom, which held that enhanced bioavailability, and reduced dosages, could be achieved only by diluting fenofibrate in binder. Instead, the claimed compositions achieve greater bioavailability by increasing the mass ratio of fenofibrate relative to binder. This results in lower effective doses, which reduces potential side effects and promotes patient compliance.

Second, the claimed compositions have surprisingly greater bioavailability compared to commercial fenofibrate formulations. In both single dose studies and at steady state, the claimed fenofibrate formulations showed greater bioavailability on a

per-milligram basis as compared to commercial formulations covered by the '726 patent and the '670 patent.

In view of the foregoing amendments and remarks, applicants request reconsideration and withdrawal of all outstanding rejections in favor of a formal notification of allowance. If, however, the Examiner perceives any impediments to such notification of allowance, whether formal or substantive, Applicants encourage the Examiner to call their attorney at the number provided below. Such informal communication will expedite examination and disposal of the application.

Respectfully submitted,

BUCHANAN INGERSOLL PC (INCLUDING ATTORNEYS FROM
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